

REMARKS

Claims 1, 3-5, 19-34, and 37-40 are pending in the present application. Among them, Claims 3, 28, and 29 are directed to non-elected species, and are withdrawn from further consideration. Applicants reserve the right to request rejoinder of claims directed to non-elected species. Applicants have canceled claim 20 without prejudice. Applicants have added new claims 42 and 43 and amended claim 1 to specify that said adzyme comprises an amino acid substitution or posttranslation modification to inhibit cleavage by said protease domain.

Support for the amendment to claim 1 and for new claim 42 can be found, for example, in paragraphs [0416], [0417], and [0420] of the published specification. Support for new claim 43, which specifies that the substrate polypeptide is found in an insoluble protein-containing aggregate, can be found, for example, in paragraph [0224]. No new matter has been entered.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Claim Rejections under 35 U.S.C. § 112, 2nd paragraph

Claims 1, 4-5, 19-27, 30-34 and 37-40 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants traverse.

Claims 1 and claims 4-5, 19-27, 30-34, and 37-40 (which depend from claim 1) are rejected due to recitation of "address site" in claim 1 because the Examiner alleges that the term "address site" is unclear and the use of "address" is confusing. Applicants respectfully traverse the rejection, because the terms "address site" and "address" and the use of these terms are well-characterized throughout the specification, for example, in paragraphs [0107] and [0201]:

[0107] The targeting moiety (or "address") is a moiety capable of recognizing and reversibly binding to a pre-determined "address binding site" (also herein "address site"), such as, for example, a soluble or membrane-bound biomolecules, or a component of a biomolecular accretion (e.g., a plaque or other insoluble protein-containing aggregate).

[0201] ...the targeting moiety reversibly binds to a pre-determined feature ("address site") associated with the targeted substrate. The targeting moiety presents one or more surfaces having chemical characteristics (e.g., hydrophobic, steric and/or ionic) which permit it to bind selectively, or relatively selectively, with the address site. In many embodiments, the address will be a modular protein (including peptide) domain which is provided in association with the catalytic domain. For example, the targeting moiety can be an antibody, or a fragment of an antibody which retains the ability to bind to the address site.

In view of the clear guidance provided in the specification, Applicants assert that the meaning of "address site" is clear and definite. One of skill in the art can readily understand the metes and bounds of the claimed invention. Nevertheless and solely to expedite prosecution, Applicants have amended claim 1, as suggested by the Examiner, to delete reference to "address". Applicants' amendment is not in acquiescence to the rejection, and Applicants reserve the right to advance additional arguments in this or future applications. Moreover, Applicants' amendment is not believed to narrow the scope of the claims, but is intended solely to improve the clarity of the claims. Applicants' amendment is believed to obviate the rejection.

Claim 1 is also rejected due to recitation of the phrase "resistant to cleavage by said protease domain". According to the Examiner, the term "resistant" is a term of degree, and it is unclear how much cleavage is required for the adzyme to be considered "resistant." Applicants respectfully traverse, but have amended claim 1 solely to expedite prosecution. As amended, claim 1 points out that the adzyme comprises an amino acid substitution or posttranslation modification to inhibit cleavage by said protease domain. Applicants' amendment is not in acquiescence to the rejection. Applicants' maintain the arguments of record regarding the acceptability of relative claim language, and Applicants expressly reserve the right to prosecute claims using the same or similar terminology in future applications. Applicants' amendment is believed to obviate the rejection.

Claim 20 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of "the adzyme is resistant to autocatalyzed proteolysis at a concentration equal to ..." because the Examiner asserts that such limitation does not further limit the subject matter of the claim from which it depends. Claim 20 is further rejected due to recitation of the phrase "resistant to autocatalyzed ...", because the Examiner alleges that "resistant" is a term of degree,

and the resulting claim does not set forth the metes and bounds of the desired patent protection. Applicants respectfully traverse.

Applicants maintain the arguments of record regarding the acceptability of relative terminology. The Examiner has not addressed Applicants' arguments, but rather, has merely made the conclusory statement that the arguments are unpersuasive. Nevertheless, Applicants have cancelled claim 20 as no longer necessary and largely redundant with claim 1, as amended. Cancellation of claim 20 is not in acquiescence to the propriety of the rejection. Applicants expressly reserve the right to present claims using the same or similar relative terminology in future applications.

In view of the foregoing arguments and amendments, Applicants contend that the pending claims are fully compliant with 35 U.S.C. § 112, second paragraph. Reconsideration and withdrawal of this rejection are requested.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 1, 4, 19-27, 30-34 and 37 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of the combined teachings of Davis et al. (WO 00/64485, hereinafter "Davis") and Chamow et al. (Trend Biotech, 1996, 14, pp. 52-60, hereinafter "Chamow"). The Examiner asserts that Davis teaches fusion proteins that have greater catalytic activity than the unconjugated molecule and Chamow teaches bispecific immunoadhesins (immunoglobulin fusion protein) comprising two different proteins having different functions each conjugated to a constant region of an immunoglobulin. Allegedly, one of skill in the art would have been motivated to make the claimed invention based on the teachings of these references. Applicants traverse.

MPEP §§ 2142-2143 set out criteria for establishing a *prima facie* case of obviousness for combining prior art reference teachings to arrive at the claimed invention. The Examiner's proposed combination of Davis and Chamow fails to establish a *prima facie* case of obviousness for, at least, the reasons of record. Nevertheless, to expedite prosecution, Applicants have

amended the claims to more particularly point out certain embodiments of the claimed adzymes. Applicants' amendment is not in acquiescence to the rejection or any of the arguments advanced by the Examiner. Applicants expressly reserve the right to prosecute claims of similar or differing scope and to present additional arguments or evidence to address the Examiner's rejections to the previously pending claims. Applicants' amendment is believed to obviate the rejection, as described briefly below.

To render the claimed invention obvious, the combined teachings of the cited references must teach each and every element of the claims. Further, one of skill in the art must have a motivation to combine the cited references in an attempt to arrive at the claimed invention, as well as a reasonable expectation of successfully doing so. Applicants contend that these criteria are not met. For example, the combined teachings of Davis and Chamow fail to teach or suggest *adzymes comprising at least one amino acid substitution or posttranslation modification to inhibit auto-cleavage by said protease domain*.

Applicants note that the prior Office Action agrees that Davis "does not teach the fusion proteins that are resistant to autoproteolytic cleavage". See page 5. The Examiner does go on to allege that, because these proteins show protease activity, they must be resistant to self cleavage. However, even assuming that the Examiner's statement is true (a point we do not concede) such a conclusion about the alleged inherent features of Davis does not provide any teaching or suggestion that protease resistance is a result of *at least one amino acid substitution or posttranslation modification*. Given that, at least, this feature of the claimed invention is neither taught nor suggested by Davis or Chamow, the cited references fail to satisfy the criteria necessary to render the claimed invention obvious.

Not only does the combination of Davis and Chamow lack all the limitations of the claims, but Applicants submit that one of skill lacks motivation to combine the references. Applicants maintain the arguments of record on this point.

The Examiner appears to have hand-picked elements of the claims from a variety of sources in the literature in order to arrive at the present claims. However, in doing so, the Examiner has failed to provide a motivation for selecting the particular combination of elements

set forth in the claims. Instead, it appears that the Examiner has started from the claimed invention and then identified prior art references that recite similar words or share certain categories of features. This is insufficient to undermine the patentability of the claimed invention. Moreover, this approach represents impermissible hindsight. MPEP 2142.

Knowledge of applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art.

Applicants assert that the Examiner has not established a *prima facie* case of obviousness. There is no motivation to combine the fundamentally distinct teachings of Davis and Chamow to arrive at the claimed invention. Moreover, the cited references fail to teach or suggest each and every limitation of the claimed invention. Accordingly, Applicants respectfully request withdrawal of the rejection.

Applicants take this opportunity to address another deficiency of the instant obviousness rejection. On page 8 of the Office Action, the Examiner asserted that the cited references "meets all of the structure limitations of the claimed invention and the additional limitations in claims 4, 21-22, and 30-34 appears to be intended uses of the claimed invention. Intended use limitations do not carry a patentable weight." Applicants respectfully disagree with the Examiner's conclusory statement that the limitations of claims 4, 21-22, and 30-34 are merely intended use limitations. For example, claim 4 more particularly points out the identity of the protease domain, and claims 21-22, and 30 more particularly point out the substrate for the adzyme. Given that the targeting moiety of the adzyme binds to the substrate, claim limitations that specify the substrate necessarily provide further structural description of the targeting moiety of the adzyme. Thus, dependent claims that further limit the claims by specifying features of the substrate do impart structural description to those dependent claims. Given that Applicants' dependent claims include features that are not merely statements of intended use, but rather do further limit the scope of the claims, Applicants submit that these claims must be either indicated

as non-obvious or addressed as part of the Examiner's obviousness analysis. In the event that the Examiner elects to maintain the instant obviousness rejection despite the detailed arguments provided above, and in the event that the Examiner elects to apply this rejection to claims 4, 21-22, and 30-34, Applicants submit that such a rejection should be made in a non-final Office Action.

Claim 5 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Davis in view of Chamow as applied to claims 1, 4, 19-27, 30-34 and 37 above, and further in view of Dolinar et al. (*Food technol and biotech.* 2000, 38, 5-9, hereinafter "Dolinar"). The Examiner asserts that Dolinar, which relates to the reversible protease inhibitor MMTS (methyl methane-thiosulfate) and refolding of a cysteine proteinase type protein, would be combined with the other references to arrive at a fusion protein complex comprising a protease using a protease inhibitor so that said fusion protein complex would not be cleaved by the protease. Applicants traverse.

As discussed above, the cited references fail to undermine the patentability of the claimed invention for, at least, failing to teach each and every element of the claims. The teachings of Dolinar do not overcome these deficiencies. If an independent claim, for example independent claim 1, is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom (e.g., claim 5) is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Accordingly, reconsideration and withdrawal of this rejection are requested.

Claims 38-40 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Davis in view of Chamow as applied to claims 1, 4, 19-27, 30-34 and 37 above, and further in view of Sanderson et al. (*Medic. Res. Rev.* 1999, 19, 179-197, hereinafter "Sanderson"). The Examiner asserts that Sanderson teaches a small molecule non-covalent binding protease inhibitor used in a pharmaceutical composition which is reversible and safe to humans. Allegedly, one of skill would be motivated to add such a protease inhibitor to a pharmaceutical

composition comprising "an adzyme of Davis et al. and Chamow et al...as taught by Sanderson et al. to extend the shelf life of the adzyme." Applicants traverse.

As discussed above, the cited references fail to undermine the patentability of the claimed invention for, at least, failing to teach each and every element of the claims. The teachings of Sanderson do not overcome these deficiencies. If an independent claim, for example independent claim 1, is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom (e.g., claim 38-40) is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Accordingly, reconsideration and withdrawal of this rejection are requested.

Double Patenting Rejection

Applicants note with appreciation that the provisional double patenting rejection over co-pending application 10/650,592 has been withdrawn.

Applicants note that the provisional double patenting rejection over co-pending application 10/792,498 has been maintained. As acknowledged by the Examiner and pursuant to MPEP 804, "[i]f the 'provisional' double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent [without filing a terminal disclaimer], thereby converting the 'provisional' double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent."

Applicants note that no claim has, as yet, been allowed in this or co-pending application Nos. 10/792,498. Applicants will consider amendments to the claims or a terminal disclaimer, if necessary, upon indication of allowable subject matter.

Co-Pending Applications

The following co-pending, commonly assigned applications are brought to the Examiner's attention: application serial number 10/792,498 and 10/650,592. The Examiner is obviously aware of the existence of these applications as they are used in the above outlined

double patenting rejection. The Examiner is invited to consider all past, present, and future prosecution in these co-pending applications.

CONCLUSION

Applicants submit that the application is in condition for allowance.

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. The Director is hereby authorized to charge any other deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. **18-1945**, from which the undersigned is authorized to draw under Order No. **COTH-P02-001**.

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